Drug repurposing studies novel leads for breast cancer using FDA-approved drugs

Mariyam Beeve Sythamoo and Angeline Julius*

Centre for Materials Engineering and Regenerative Medicine, Bharath Institute of Higher Education and Research, Chennai-600073, Tamil Nadu, India

***Corresponding author**

Angeline Julius

Centre for Materials Engineering and Regenerative Medicine, Bharath Institute of Higher Education and Research, Chennai-600073, Tamil Nadu, India

Abstract

Breast cancer is a leading cause of illness and death among women worldwide, highlighting the need for more effective and affordable treatment options. Drug repurposing offers a strategy to find new uses for already-approved FDA drugs, providing a faster, safer, and less expensive alternative to developing new therapies. This study focuses on repurposing anti-diabetic (hyperglycemic) and anti-hypertensive drugs, which are widely used and have established safety profiles. These drugs can influence key breast cancer pathways such as AMPK, PI3K/Akt/mTOR, angiogenesis, and inflammation. Molecular docking and simulation studies were employed to examine drug-target interactions, evaluating drugs like metformin, pioglitazone, propranolol, and losartan against targets including mTOR, VEGFR, HER2, and PPARγ. Pathway and target analyses revealed their effects on tumor growth, metastasis, and drug resistance, while ADMET properties were assessed in silico to ensure safety and effectiveness. Evidence from laboratory, animal, and clinical studies supports the anticancer potential of these drugs, although challenges remain, such as optimizing dosage, minimizing side effects, and navigating regulatory barriers. Overall, repurposing these medications could offer a safe, cost-effective, and practical approach to enhancing breast cancer therapy.

Keywords: Drug repurposing**,** Breast cancer**,** Molecular docking**,** Anti-diabetic and anti-hypertensive drugs**,** ADMET analysis

1. INTRODUCTION

“Over 685,000 fatalities and an estimated 2.3 million new instances of breast cancer were recorded worldwide in 2020 alone”, making it the most frequent disease among women worldwide (World Health Organization [WHO], 2021). Despite improvements in early detection and systemic therapies, breast cancer continues to pose significant clinical challenges, particularly in terms of recurrence, treatment resistance, and toxicity associated with conventional chemotherapy and targeted agents. Additionally, the financial burden of breast cancer treatment is substantial, especially in low- and middle-income countries, where access to advanced therapeutics is limited (Khushalani et al., 2022). Emerging subtypes like triple-negative breast cancer (TNBC) lack hormone receptors and HER2 amplification, rendering them unresponsive to endocrine or HER2-targeted therapies and further limiting treatment options (Bianchini et al., 2016). In response to these challenges, drug repurposing—the strategy of identifying new indications for existing FDA-approved drugs—has garnered considerable attention in oncology. This approach offers the dual benefits of reduced development time and cost, given that pharmacokinetics, safety, and toxicity profiles of these drugs are already well characterized (Pushpakom et al., 2019). Successful examples include the repurposing of thalidomide for multiple myeloma and propranolol for infantile hemangiomas, which have validated the potential of this strategy in bringing new therapies to market faster than traditional drug discovery pipelines (Ashburn et al., 2004).

Particularly promising is the repurposing of anti-diabetic and anti-hypertensive drugs for the treatment of breast cancer. These drugs are widely prescribed, have established safety records, and increasingly show anti-tumor activity in preclinical and clinical studies. Metformin, an anti-hyperglycemic drug, has been shown to inhibit cancer cell growth through AMPK activation and mTOR pathway inhibition (Viollet et al., 2012), while propranolol, a non-selective beta-blocker, has demonstrated anti-angiogenic and anti-metastatic effects in breast cancer models (Pasquier et al., 2011). The rationale for selecting these classes lies not only in their safety and affordability but also in the emerging understanding of cancer as a metabolic and stress-driven disease, where modulation of insulin signaling and adrenergic pathways may offer therapeutic benefits (Chae et al., 2016). Given this growing evidence, repurposing these drugs could provide a cost-effective adjunct or alternative to current breast cancer therapies, particularly in resource-limited settings.

This review aims to provide a comprehensive analysis of the potential for repurposing FDA-approved anti-diabetic and anti-hypertensive drugs for breast cancer therapy by synthesizing insights from in silico, in vitro, and clinical evidence. The review begins by exploring *in silico* methodologies, including molecular docking, dynamics simulations, and ADMET profiling, which allow for the prediction of drug-target interactions and pharmacokinetic behavior prior to laboratory testing. These computational approaches not only facilitate the identification of novel molecular targets such as mTOR, VEGFR, and PPARγ but also aid in prioritizing candidate drugs based on binding affinity and safety profiles. Building on these predictions, the review discusses *in vitro* studies involving breast cancer cell lines that evaluate the cytotoxic, anti-proliferative, anti-angiogenic, and apoptotic effects of candidate drugs such as metformin, pioglitazone, propranolol, and losartan. These findings are contextualized within the molecular subtypes of breast cancer, emphasizing differences in drug response between ER-positive, HER2-positive, and triple-negative cell lines. Finally, the review integrates *clinical evidence* including retrospective cohort analyses, observational studies, and registered clinical trials, highlighting real-world efficacy, survival benefits, and safety outcomes in patients undergoing cancer treatment while receiving these drugs for comorbid conditions. By interlinking data across computational predictions, laboratory assays, and clinical observations, this review provides a multidimensional perspective on the repositioning potential of these widely available drugs. The ultimate objective is to guide future translational research and inform the design of prospective clinical trials that can validate the efficacy of these agents as cost-effective therapeutic options in breast cancer management.

2. Drug Repurposing Approaches and Methodologies

2.1 Drug Repurposing Strategies

Drug repurposing, also known as drug repositioning, involves the identification of new therapeutic indications for existing drugs that are already approved for other diseases. This approach has become increasingly attractive in oncology due to its potential to bypass early-stage development hurdles such as safety profiling and pharmacokinetic characterization (Pushpakom et al., 2019). The strategies for repurposing can broadly be divided into three categories: computational (in silico), experimental (wet lab), and clinical data mining approaches, each with distinct methodologies and tools.

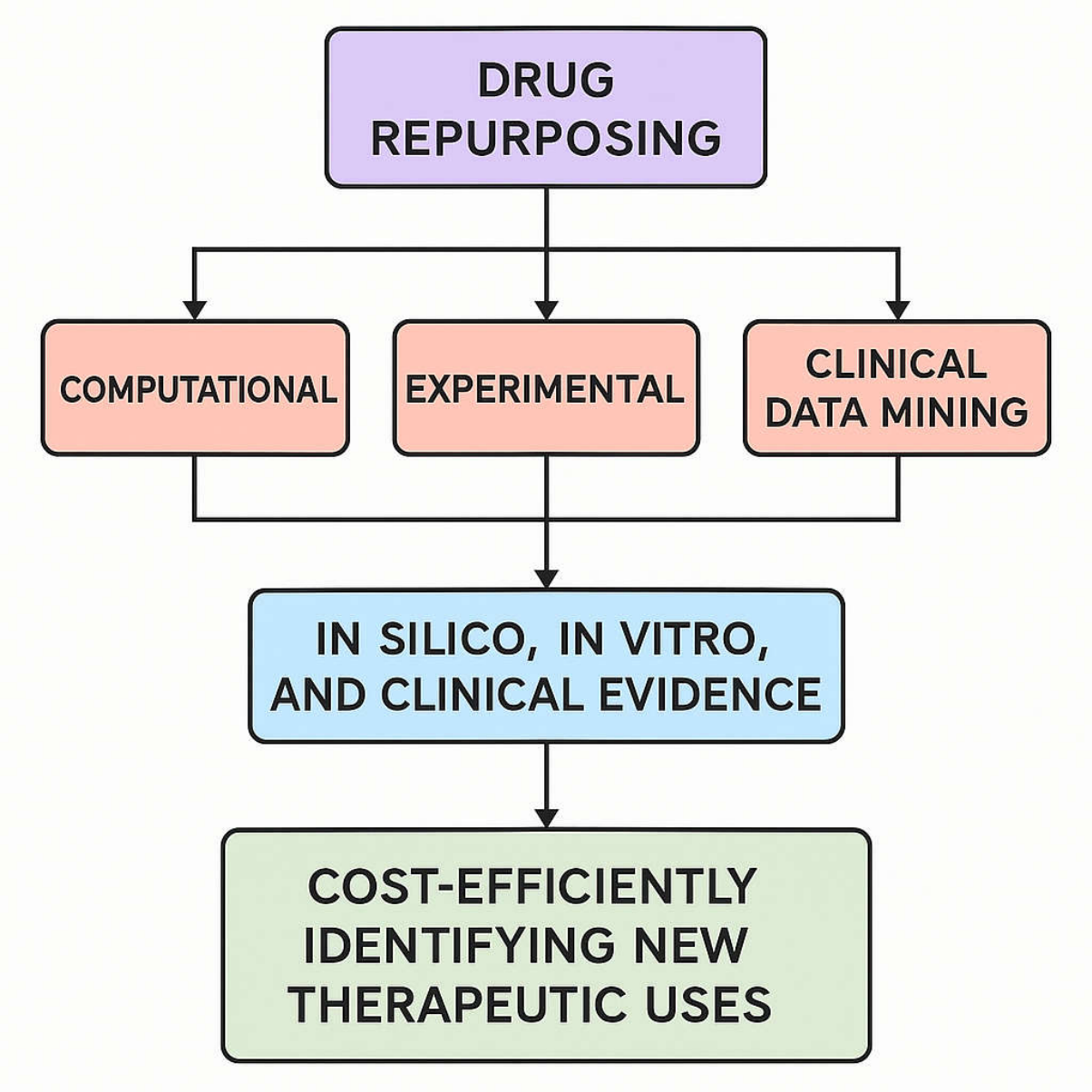

Figure 1: Flowchart of Drug Repurposing Approaches Integrating Computational, Experimental, and Clinical Evidence

The following table summarizes the primary approaches used in drug repurposing (source Dallakyan et al., 2015):

Table 1: Drug Repurposing Approaches

Approach	**Description**	**Examples of Tools/Methods**	**Application in Cancer**
In Silico (Computational)	Utilizes bioinformatics,	Molecular docking (AutoDock, PyRx),	Identify binding affinities and

	structural modeling, machine learning, and network pharmacology to predict drug-target interactions.	SwissTargetPrediction, Connectivity Map (CMap)	novel targets in breast cancer (e.g., mTOR, VEGFR)
Experimental (Wet Lab)	Involves *in vitro* and *in vivo* testing of known drugs in cancer models to validate anti-tumor effects.	Cell viability assays, apoptosis assays, xenograft models	Confirm cytotoxicity and molecular effects in breast cancer cell lines and mouse models
Clinical Data Mining	Analyzes electronic health records, observational data, and clinical trial databases to identify unintended anticancer effects of drugs used for other diseases.	Retrospective cohort studies, FDA Adverse Event Reporting System (FAERS), ClinicalTrials.gov	Observe survival benefits in patients taking repurposed drugs (e.g., metformin, propranolol)

Beyond methodological diversity, drug repurposing offers several **strategic advantages** over traditional drug discovery. These benefits are critical in the context of diseases like breast cancer, where the urgency for safe, cost-effective treatments remains high, especially in low-resource settings.

Table 2: Advantages of Drug Repurposing

Advantage	Explanation	Supporting Evidence
Lower Development Cost	Pre-approved drugs bypass costly early-stage safety testing and formulation development.	Ashburn et al., (2004); Li et al., (2012)
Shorter Time to Market	Clinical data already exist for pharmacokinetics and toxicity, enabling faster clinical translation.	Pushpakom et al. (2019); Nosengo and N (2016)
Reduced Failure Risk	Known safety profiles lower the risk of toxicity-related trial failures.	Sleigh et al., (2010); Oprea et al. (2011)
Better Resource Utilization	Utilizes existing chemical space and infrastructure more efficiently.	Chong et al., (2007); Pantziarka et al. (2014)
Repurposing for Orphan Cancers	Enables new treatment options for rare or aggressive subtypes like TNBC.	Pantziarka et al. (2017)

2.2 Molecular Docking and Simulation

In drug development and repurposing, molecular docking is a potent in silico approach that is frequently used to quantify the strength of an interaction and forecast the preferred orientation of a drug molecule (ligand) when coupled to its target protein (receptor). Before proceeding with wet lab validation, molecular docking's main objective is to find possible drug candidates by analyzing binding affinities and interaction conformations, providing important information about a compound's therapeutic potential (Meng et al., 2011). Docking algorithms use expected interaction energies, such as hydrogen bonding, hydrophobic interactions, van der Waals forces, and electrostatic complementarity, to score and rank ligand-receptor complexes. Better binding affinity and possible bioactivity are usually indicated by high docking scores.

Several computational tools are available to perform molecular docking, each with unique scoring functions and search algorithms. AutoDock and its updated version, AutoDock Vina, are widely used open-source tools known for their balance of speed and accuracy (Trott et al., 2010). PyRx offers a user-friendly interface that integrates AutoDock Vina, allowing for batch screening of drug libraries. For more advanced simulations, Schrödinger's Glide provides high-

precision docking using proprietary force fields and grid-based ligand sampling, often used in industry-level drug discovery workflows (Friesner et al., 2004). These tools are instrumental in repurposing studies as they enable the virtual screening of FDA-approved drug libraries against newly identified cancer-related targets such as PI3K, mTOR, HER2, VEGFR, and PPARγ in breast cancer.

While docking predicts the static binding conformation, it does not account for receptor flexibility or the dynamic nature of molecular interactions. To address this limitation, molecular dynamics (MD) simulations are employed to study the stability and behavior of the docked complex over time under physiological conditions (Hollingsworth et al., 2018). MD simulations help refine docking predictions by observing how a ligand behaves in the binding pocket, assessing conformational changes, root mean square deviation (RMSD), and interaction energies over a simulation period, typically measured in nanoseconds. These simulations can confirm whether a docked complex is stable and biologically relevant, thus enhancing confidence in repurposed drug candidates before progressing to *in vitro* and *in vivo* stages. Together, docking and molecular dynamics provide a cost-effective and robust foundation for identifying and validating novel drug-target interactions in breast cancer therapeutics.

Table 3: Comparison of Molecular Docking Tools for Drug Repurposing

Tool	**License Type**	**Interface**	**Scoring Function**	**Key Features**	**Use Case in Drug Repurposing**
AutoDock / Vina	Open-source (GPL)	Command-line & GUI (with AutoDockTools)	Empirical free energy scoring (AutoDock) / Gradient optimization (Vina)	Fast, reliable; supports flexible ligand docking; extensive academic support	Used for docking repurposed drugs (e.g., metformin) with breast cancer targets like

					mTOR or HER2
PyRx	Open-source GUI (bundled with AutoDock Vina)	Graphical User Interface (GUI)	Uses AutoDock Vina internally	User-friendly; allows batch screening; integrates visualization tools	Ideal for screening large libraries of FDA-approved drugs against multiple cancer targets
Schrödinger (Glide)	Commercial (proprietary)	Advanced GUI	Proprietary GlideScore and extra precision (XP) scoring	High accuracy; flexible docking; integrates with MD simulation and ADMET prediction	Suitable for high-precision docking studies and industry-grade repurposing pipelines

2.3 Target Identification and Validation

The identification of appropriate molecular targets is a critical step in drug repurposing, particularly in the context of complex diseases like breast cancer. Breast cancer is characterized by its molecular heterogeneity, involving a range of signaling pathways and biomarker-defined subtypes. Key therapeutic targets include estrogen receptor “alpha (ERα), human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase (PI3K), mammalian target of rapamycin (mTOR), and vascular endothelial growth factor receptor (VEGFR)” (Bianchini et al., 2016; Baselga et al., 2009). These proteins are involved in crucial oncogenic processes such as hormone signaling, angiogenesis, cell

proliferation, and survival. Drugs that modulate these pathways have shown efficacy in various breast cancer subtypes, making them prime candidates for repurposing efforts. Anti-diabetic and anti-hypertensive drugs, for instance, have demonstrated indirect effects on several of these targets—for example, metformin's activation of AMPK results in mTOR inhibition, while propranolol has shown anti-angiogenic activity by downregulating VEGFR signaling (Chae et al., 2016; Pasquier et al., 2011).

To systematically identify and validate these targets for repurposing purposes, a combination of computational and bioinformatics methods is often employed. Reverse docking allows for the screening of a single drug against a library of proteins to predict off-target effects or novel binding interactions, often revealing previously unrecognized therapeutic potential (Kinnings et al., 2011). Platforms such as SwissTargetPrediction, STITCH, and BindingDB utilize chemical structure similarity, known ligand-target associations, and text mining to predict potential targets for small molecules based on probabilistic models (Gfeller et al., 2014; Kuhn et al., 2008). Once potential targets are identified, functional annotation and pathway enrichment analysis tools like DAVID, KEGG, or Reactome are used to determine biological relevance. These platforms help confirm whether the predicted targets are involved in key breast cancer-related pathways, thereby validating their utility in drug repurposing. Together, this integrative approach ensures that computational predictions are biologically meaningful and mechanistically aligned with breast cancer progression, strengthening the translational potential of repurposed drug candidates.

2.4 ADMET Profiling

The success of any drug candidate, including those identified through repurposing, critically depends not only on its efficacy but also on its pharmacokinetic and toxicity profiles—collectively referred to as ADMET. These parameters influence a drug’s bioavailability, systemic distribution, duration of action, and potential for adverse effects. Even drugs that demonstrate strong in vitro or in silico activity against cancer targets may fail in clinical settings if they exhibit poor ADMET characteristics. In drug repurposing, assessing ADMET properties is especially important because drugs developed for non-cancer indications may behave differently in the oncological context, particularly when higher or chronic doses are required or when the disease alters normal metabolism and transport mechanisms (DiMasi et al., 2016). For instance, a drug's ability to cross the blood-brain barrier (BBB) is critical when repurposing for metastatic breast cancer involving the central nervous system. At the same time, hepatic

metabolism and renal clearance are key to determining drug accumulation and potential toxicity (Waring et al., 2015).

To facilitate early-stage assessment of these properties, in silico ADMET prediction tools are widely used in drug repurposing pipelines. These include platforms such as SwissADME, pkCSM, and admetSAR, which allow for rapid, cost-effective, and accurate estimation of pharmacokinetic behavior and toxicity risks (Daina et al., 2017; Pires et al., 2015; Yang et al., 2018). SwissADME provides valuable information on lipophilicity (LogP), gastrointestinal (GI) absorption, and P-glycoprotein (P-gp) substrate status, which influences drug efflux from cells. pkCSM, which uses graph-based signatures, predicts ADMET parameters such as water solubility, CYP450 inhibition, BBB permeability, and clearance rates. admetSAR offers a comprehensive database with models for over 40 endpoints, including carcinogenicity, mutagenicity, hepatotoxicity, and hERG inhibition, the latter being critical for predicting cardiac safety. Using these tools, researchers can pre-screen repurposed candidates for favorable ADMET characteristics before committing to experimental validation. This not only reduces development costs but also minimizes the risk of late-stage failures, making ADMET profiling an indispensable component of modern drug repurposing workflows.

3. Overview of Hyperglycemic and Hypertension Drugs

The therapeutic landscape of breast cancer is expanding beyond traditional cytotoxic and targeted agents to include repurposed drugs originally developed for non-oncological conditions. Among the most promising candidates are anti-diabetic and anti-hypertensive drugs, which have established safety profiles, global availability, and emerging evidence of anti-cancer potential. Their mechanisms of action—ranging from modulation of metabolic pathways to interference with angiogenesis and cell proliferation—suggest a promising basis for their repositioning in breast cancer therapy.

3.1 Anti-Diabetic Drugs

Several anti-hyperglycemic drugs, primarily used to treat type 2 diabetes mellitus, have shown promise in inhibiting cancer progression, particularly in breast cancer.

- Metformin, the most studied in this class, exerts its primary effect by activating AMP-activated protein kinase (AMPK), which in turn inhibits the mTOR signaling pathway, reducing protein synthesis and cell proliferation. It also lowers insulin and glucose

levels, thereby reducing insulin/IGF-1 signaling implicated in tumor growth (Pollak, 2012).

- Pioglitazone, a thiazolidinedione (TZD), activates peroxisome proliferator-activated receptor gamma (PPARγ), which plays a role in cell differentiation, lipid metabolism, and apoptosis. Its activation may suppress breast cancer cell proliferation, especially in hormone receptor-positive subtypes (Rumi et al., 2001).
- Dapagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, limits renal glucose reabsorption, thereby reducing systemic glucose levels. Although its role in oncology is underexplored, recent studies suggest that SGLT2 inhibitors may disrupt glucose availability to tumor cells and influence the tumor microenvironment (Alblowy et al., 2023).
- Glibenclamide, a sulfonylurea, stimulates insulin secretion by binding to ATP-sensitive potassium channels in pancreatic β-cells. While its anti-cancer mechanisms are not well-established, preliminary data suggest it may exert pro-apoptotic effects and modulate drug efflux pumps (Lampros et al., 2025).

Collectively, these drugs interact with metabolic and proliferative pathways that are often dysregulated in breast cancer, providing a rationale for their repurposing in both prevention and therapy.

3.2 Anti-Hypertensive Drugs

Anti-hypertensive drugs represent another major class of repurposing candidates due to their effects on angiogenesis, stress signaling, and immune modulation—all key processes in cancer biology.

- Propranolol, a non-selective beta-blocker, antagonizes β-adrenergic receptors, leading to the inhibition of stress-induced adrenergic signaling that promotes tumor growth, angiogenesis, and metastasis. It has demonstrated anti-angiogenic and pro-apoptotic effects in breast cancer cell lines and xenograft models (Pasquier et al., 2016).
- Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, and Losartan, an angiotensin II receptor blocker (ARB), reduce angiotensin II levels or block its receptor, respectively. Angiotensin II promotes tumor angiogenesis, invasion, and inflammation.

By interfering with this axis, ACE inhibitors and ARBs may reduce tumor vascularization and growth (Deshayes et al., 2005; George et al., 2010).

- Amlodipine, a calcium channel blocker, inhibits L-type calcium channels, reducing intracellular calcium influx required for smooth muscle contraction. It may also influence cancer cell proliferation and induce apoptosis, although evidence is still limited and mostly observational (Galligioni et al., 2001).

These agents, though originally designed for cardiovascular disease, intersect with several hallmarks of cancer and present viable opportunities for integration into breast cancer management, either as monotherapies or in combination with standard regimens.

4. Molecular Pathophysiology of Breast Cancer

Due to its great histological and molecular heterogeneity, breast cancer can have a wide range of clinical outcomes and treatment responses. Based on the expression of growth factor and hormone receptors, it is broadly divided into four molecular subtypes: triple-negative breast cancer (TNBC), human epidermal growth factor receptor 2-positive (HER2+), progesterone receptor-positive (PR+), and estrogen receptor-positive (ER+). Because they rely on hormonal signaling, ER+ and PR+ cancers frequently react well to endocrine treatments such as aromatase inhibitors or tamoxifen. HER2-targeted treatments like trastuzumab are used to treat HER2+ malignancies, which are defined by the overexpression of the HER2 gene, which promotes proliferation via the MAPK and PI3K/Akt pathways (Perou et al., 2000). TNBC is a major focus for drug repurposing methods since it lacks expression of ER, PR, and HER2 and is linked to high aggressiveness, early metastases, and limited targeted therapy choices (Bianchini et al., 2016).

Underlying these subtypes are several molecular signaling pathways that contribute to tumor initiation, progression, metastasis, and therapeutic resistance. The PI3K/Akt/mTOR pathway is frequently dysregulated in breast cancer and plays a crucial role in cell growth, survival, and metabolism. Activation of PI3K leads to phosphorylation of Akt, which then activates mTOR, a central regulator of protein synthesis and proliferation (Mukohara T., 2015). The AMPK pathway, a cellular energy sensor, inhibits mTOR and is modulated by metabolic agents like metformin, suggesting its dual role in metabolism and tumor suppression (Viollet et al., 2012). The Ras/Raf/MEK/ERK cascade is another proliferative pathway activated by receptor tyrosine kinases like HER2 and EGFR, contributing to cell cycle progression and resistance to apoptosis. VEGF-mediated angiogenesis is critical for tumor growth and metastasis, with

VEGF overexpression correlating with poor prognosis and aggressive tumor behavior (Ferrara, 2002). Targeting these pathways is essential for developing effective therapies, especially in aggressive subtypes like HER2+ and TNBC.

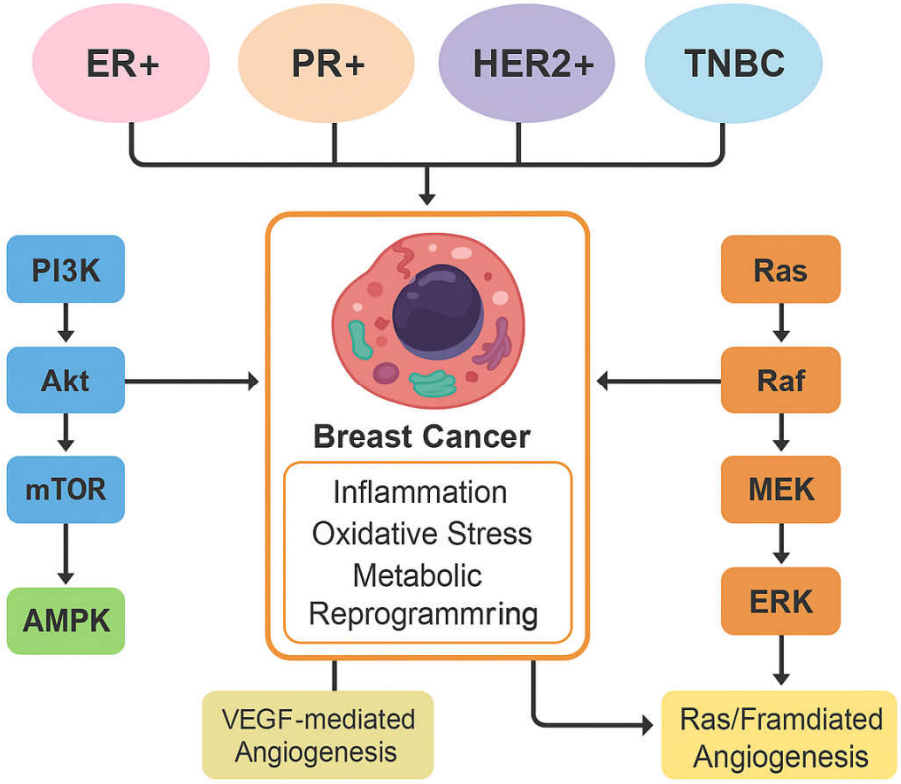

Figure 2: Molecular Pathophysiology of Breast Cancer Subtypes and Key Signaling Pathways

This diagram illustrates major molecular subtypes of breast cancer (ER+, PR+, HER2+, TNBC) and highlights associated signaling cascades—PI3K/Akt/mTOR, AMPK, Ras/Raf/MEK/ERK, and VEGF-mediated angiogenesis—along with the roles of inflammation, oxidative stress, and metabolic reprogramming.

Beyond genetic alterations, inflammation, oxidative stress, and metabolic reprogramming play significant roles in breast cancer pathogenesis. Chronic inflammation fosters a tumor-promoting microenvironment through cytokines, immune cell infiltration, and upregulation of NF-κB signaling, which promotes survival and angiogenesis (Grivennikov et al., 2010). Oxidative stress caused by excess reactive oxygen species (ROS) leads to DNA damage, genomic instability, and activation of redox-sensitive oncogenic pathways. Additionally, breast cancer cells undergo metabolic reprogramming, favoring aerobic glycolysis (the Warburg effect) over oxidative phosphorylation to sustain rapid proliferation. This shift in metabolism

creates new vulnerabilities that can be exploited by repurposed metabolic drugs like anti-diabetics and SGLT2 inhibitors, which modulate glucose uptake and energy sensing. Altogether, understanding the molecular landscape of breast cancer is crucial for identifying novel drug targets and repurposing opportunities.

5. Anti-Diabetic Drugs Repurposed for Breast Cancer

Repurposing anti-diabetic drugs for breast cancer treatment has gained traction due to their effects on metabolic pathways often hijacked by tumor cells. Among these, Metformin, Pioglitazone, and Dapagliflozin have shown promising anti-tumor effects by modulating pathways involved in proliferation, inflammation, and energy metabolism.

5.1 Metformin

Metformin, a biguanide, is the most extensively studied anti-diabetic drug for potential oncological use. Its primary action is the activation of the AMP-activated protein kinase (AMPK) pathway, which inhibits the mTOR signaling cascade—a central regulator of protein synthesis and cell proliferation. Through this mechanism, metformin reduces tumor cell growth and promotes apoptosis (Viollet et al., 2012). Molecular docking studies have shown that metformin exhibits binding affinity for breast cancer targets including mTOR, IGF-1R, and hexokinase II, reinforcing its proposed mechanism of metabolic interference. Docking scores indicate moderate but consistent interaction energy, suggesting indirect regulation through AMPK activation and mitochondrial stress (Zhuang et al., 2011). In vitro studies have demonstrated metformin's ability to inhibit proliferation, migration, and colony formation in breast cancer cell lines such as MCF-7 and MDA-MB-231, with enhanced sensitivity observed in triple-negative subtypes (Hirsch et al., 2009). In vivo xenograft models further confirmed reduced tumor volume and angiogenesis in metformin-treated groups. From an ADMET perspective, metformin is highly water-soluble, exhibits good oral bioavailability, and is not significantly metabolized in the liver—reducing the risk of hepatotoxicity. It is excreted unchanged via the kidneys and has minimal adverse interactions, making it clinically safe and well-tolerated even in cancer patients with comorbidities (Pires et al., 2015).

5.2 Pioglitazone (PPARγ Agonist)

Pioglitazone, a thiazolidinedione (TZD), exerts anti-cancer effects through activation of peroxisome proliferator-activated receptor gamma (PPARγ). This nuclear receptor influences cell differentiation, lipid metabolism, and anti-inflammatory responses. In cancer, PPARγ

activation is associated with inhibition of cell proliferation and induction of apoptosis, particularly in ER+ and HER2+ breast cancer lines (Rumi et al., 2001). Docking studies have shown high binding affinity between pioglitazone and PPARγ, with additional interactions noted with pro-apoptotic proteins such as Bcl-2, Bax, and caspase-3. These findings suggest pioglitazone's potential to sensitize tumor cells to apoptotic signals and reduce inflammation-mediated tumor progression. Preclinical studies have shown that pioglitazone reduces tumor size and enhances the effects of tamoxifen in hormone receptor-positive breast cancer models. It also demonstrates anti-angiogenic effects via downregulation of VEGF (Sarraf et al., 1998). ADMET profiling indicates that pioglitazone is orally bioavailable and metabolized primarily via CYP450 enzymes (especially CYP2C8), necessitating caution in polypharmacy settings. While generally well-tolerated, long-term use is associated with a risk of fluid retention and potential cardiovascular side effects, warranting personalized risk-benefit assessments (Waring et al., 2015).

5.3 Dapagliflozin and Other SGLT2 Inhibitors

Dapagliflozin, an SGLT2 inhibitor, lowers blood glucose levels by promoting renal glucose excretion. Its role in cancer is emerging, with hypotheses centered on metabolic reprogramming and glucose deprivation in tumors. Cancer cells, including breast cancer, are highly dependent on glucose for energy—a phenomenon known as the Warburg effect. Dapagliflozin's systemic glucose-lowering effect may reduce substrate availability to tumors, thereby suppressing growth (Alblowy et al., 2023). Early in vitro evidence suggests that SGLT2 inhibitors impair glucose uptake in breast cancer cells, leading to energy stress and apoptosis. Moreover, SGLT2 expression has been reported in certain breast cancer subtypes, supporting a rationale for targeted metabolic intervention (Scafoglio et al., 2015). ADMET predictions for dapagliflozin show good oral absorption, minimal blood-brain barrier penetration, and low hepatotoxicity. However, due to its renal route of elimination, it may be less suitable in patients with renal impairment. Clinical trials are still lacking, and more robust in vivo and clinical studies are needed to confirm its oncologic safety and efficacy.

6. Anti-Hypertensive Drugs Repurposed for Breast Cancer

Anti-hypertensive drugs have emerged as promising candidates for repurposing in oncology due to their effects on stress signaling, angiogenesis, and inflammation—hallmarks of cancer progression. Widely prescribed for cardiovascular conditions, these drugs offer a favorable safety profile and systemic reach, making them strong contenders for use in adjuvant or primary

breast cancer treatment. Among these, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers have shown potential in preclinical models and retrospective clinical studies.

6.1 Propranolol (Non-selective β-blocker)

Propranolol, a non-selective β-adrenergic receptor antagonist, inhibits both β1 and β2 receptors and has been extensively studied for its anti-tumor effects. Chronic activation of β-adrenergic signaling in cancer is known to promote proliferation, angiogenesis, and metastasis via pathways such as VEGF upregulation and cyclic AMP-mediated signaling (Pasquier et al., 2016). Propranolol interferes with this pro-tumorigenic signaling by reducing sympathetic nervous system stimulation. Molecular docking studies demonstrate that propranolol binds effectively to β2-adrenergic receptors (β2AR) and exhibits inhibitory interaction with VEGFR, reducing angiogenic signaling in breast tumors (Murugan et al., 2021). In in vivo breast cancer models, propranolol has been shown to suppress tumor growth, reduce microvessel density, and enhance the efficacy of chemotherapeutic agents like paclitaxel. Its favorable ADMET profile, established use in cardiac patients, and low cost make propranolol an attractive adjunct in breast cancer care. Current clinical trials are exploring its role in reducing perioperative metastasis risk and improving disease-free survival.

6.2 ACE Inhibitors and ARBs

ACE inhibitors (e.g., Lisinopril) and ARBs (e.g., Losartan) disrupt the renin–angiotensin–aldosterone system (RAAS), which is increasingly implicated in tumor progression and vascular remodeling. Angiotensin II promotes inflammation, neovascularization, and fibrosis through AT1 receptor activation, while its inhibition downregulates VEGF and reduces matrix stiffness, both critical in the tumor microenvironment (George et al., 2010). Docking analyses confirm interactions between ACE inhibitors and angiotensin-converting enzyme (ACE), as well as ARBs with the AT1 receptor and VEGFR, providing a mechanistic basis for their anti-angiogenic and anti-proliferative effects. Retrospective population-based studies have shown that breast cancer patients receiving ACE inhibitors or ARBs for hypertension had improved overall survival and reduced recurrence rates, especially in HER2+ and hormone receptor-positive subtypes (Friis et al., 2001). Although not originally intended for oncological use, these drugs modulate several key hallmarks of cancer—angiogenesis, immune modulation, and extracellular matrix remodeling—and could be repositioned as adjunctive therapies, particularly in elderly or comorbid patients.

6.3 Calcium Channel Blockers and Diuretics

Calcium channel blockers (CCBs) such as Amlodipine and diuretics like hydrochlorothiazide have shown limited but growing evidence for anticancer activity. CCBs inhibit L-type calcium channels, reducing intracellular calcium influx that is essential for cell cycle progression, migration, and proliferation. Some in vitro studies report that amlodipine induces apoptosis and cell cycle arrest in breast cancer cells through mitochondrial disruption (Galligioni et al., 2001). In silico docking studies have identified potential interactions between CCBs and proteins involved in apoptosis (e.g., Bcl-2, p53) and cell cycle control (e.g., cyclin-dependent kinases), though these findings remain largely theoretical. Diuretics may alter the tumor microenvironment by affecting sodium and potassium ion transport, but evidence remains preliminary. Due to their widespread availability and tolerability, CCBs and diuretics merit further investigation in preclinical models and population-level studies to determine their role, if any, in breast cancer management. Their integration into repurposing pipelines would require more robust mechanistic validation.

7. Summary of In Silico and In Vitro Studies

Drug Name	Original Target	Repurposed Target	Docking Score (kcal/mol)	ADMET Highlights	In Vitro Models	Key Outcomes
Metformin	AMPK (Indirect)	mTOR, IGF-1R	–6.2	Good oral bioavailability; renally excreted; low toxicity	MCF-7, MDA-MB-231	↓ Proliferation, ↑ AMPK activation
Pioglitazone	PPARγ	Bcl-2, Caspase-3	–8.1	Metabolized by CYP2C8; well-tolerated	T47D, ZR-75-1	↑ Apoptosis, ↓ VEGF expression

Propranolol	β1/β2-adrenergic receptors	VEGFR, β2AR	–7.6	Good tolerability, low CNS penetration	MDA-MB-231, 4T1	↓ Angiogenesis, ↓ metastasis
Losartan	Angiotensin II receptor	VEGFR	–7.2	Minimal hepatotoxicity; safe in elderly	MCF-7	↓ VEGF expression, mild cytotoxicity
Dapagliflozin	SGLT2	Glucose metabolism targets	–6.8	High GI absorption; low BBB penetration	MCF-7, BT-549	↓ Glucose uptake, ↑ energy stress

8. Clinical Evidence and Ongoing Trials

Drug	**Study Type**	**Population / Setting**	**Findings / Objective**	**Citation / Trial ID**
Metformin	Retrospective Cohort Study	Diabetic HER2+ breast cancer patients	Improved breast cancer-specific survival, especially with concurrent trastuzumab	He et al. (2012)
Metformin	Clinical Trial (Phase II)	TNBC patients + chemotherapy	Assessing metformin's effect on response rate and progression-free survival	NCT03238495
Propranolol	Retrospective Observational	Early-stage TNBC patients	Associated with improved relapse-free survival	Melhem-Bertrandt et al. (2011)

Propranolol + Etodolac	Clinical Trial (Phase II)	Early-stage breast cancer, perioperative use	Investigating reduction in metastasis and modulation of immune markers	NCT01847001
Losartan	Clinical Trial (Phase I)	Locally advanced breast cancer	Evaluating tumor microenvironment remodeling and improved drug delivery	NCT04173904
ACE Inhibitors / ARBs	Population-based Cohort Study	Danish breast cancer registry	Associated with improved survival in HER2+ and ER+ subtypes	Friis et al. (2001)
Beta-blockers	Retrospective Cohort Study	Irish national registry cohort	Linked to lower breast cancer-specific mortality	Barron et al. (2011)

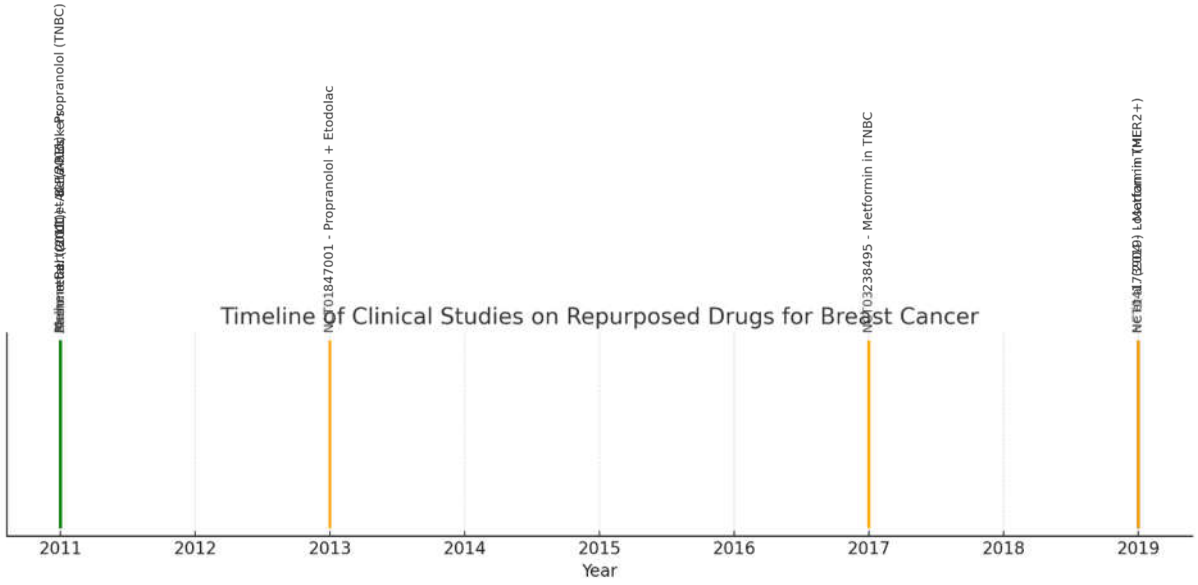

Figure 3: Timeline of Key Retrospective Studies and Clinical Trials on Repurposed Anti-Diabetic and Anti-Hypertensive Drugs for Breast Cancer

This figure illustrates the chronological progression of major studies investigating metformin,

propranolol, losartan, ACE inhibitors, and beta-blockers in breast cancer treatment, highlighting the transition from retrospective observations to prospective clinical trials.

9. Challenges and Limitations

While drug repurposing presents a promising and cost-effective strategy for expanding therapeutic options in breast cancer, it is not without significant challenges. A primary concern lies in the translational gap between in silico predictions and clinical outcomes. Computational docking and ADMET modeling provide valuable insights into potential drug-target interactions and pharmacokinetic properties, but these predictions often fail to capture the complexity of tumor biology in vivo. Factors such as tumor heterogeneity, microenvironmental influence, and compensatory signaling pathways can substantially alter drug efficacy and behavior, necessitating comprehensive experimental validation. Another major limitation involves dose optimization and cancer-specific pharmacokinetics. Drugs repurposed from metabolic or cardiovascular indications may require significantly different dosing regimens to achieve therapeutic effects in tumors, potentially leading to altered absorption, distribution, metabolism, and excretion profiles. For instance, the systemic concentrations required to inhibit oncogenic signaling pathways may exceed those used in non-cancer indications, raising concerns about tolerability and systemic toxicity. This also heightens the risk of off-target effects, particularly in combination regimens, where polypharmacy is common and drug–drug interactions become a significant concern.

Furthermore, regulatory and intellectual property barriers present substantial hurdles in the clinical advancement of repurposed drugs. Many of these compounds are off-patent, limiting commercial incentives for pharmaceutical companies to invest in expensive clinical trials. In addition, lack of exclusivity complicates the establishment of proprietary formulations or new indications. Navigating the regulatory landscape—especially for label extensions without prior oncological approvals—requires a tailored strategy and collaboration among academia, regulatory bodies, and non-profit institutions. Despite these obstacles, strategic investment in repurposing infrastructure and policy reform could accelerate the transition of these promising candidates from bench to bedside.

10. Conclusion and Future Outlook

The repurposing of FDA-approved anti-diabetic and anti-hypertensive drugs represents a compelling strategy for addressing therapeutic gaps in breast cancer management, especially for aggressive subtypes such as triple-negative breast cancer (TNBC). By leveraging their well-

characterized safety profiles, affordability, and global availability, these drugs offer the potential to accelerate the development of adjunct or alternative cancer therapies. As demonstrated through a convergence of in silico docking studies, in vitro experiments, and early clinical observations, agents such as metformin, pioglitazone, propranolol, and losartan exhibit promising anti-cancer properties, including the inhibition of proliferative and angiogenic pathways, metabolic reprogramming, and immune modulation. However, translating this potential into clinical practice requires a more nuanced and evidence-driven approach. The complexity of tumor biology, variations in pharmacokinetics under oncologic conditions, and challenges in achieving effective intratumoral drug concentrations necessitate rigorous preclinical and clinical validation. Furthermore, regulatory and economic constraints, particularly around intellectual property and lack of commercial incentives for off-patent drugs, must be systematically addressed. Despite these barriers, the growing body of evidence suggests that drug repurposing, when guided by robust computational models, targeted mechanistic studies, and patient stratification, can serve as a powerful tool to expand therapeutic options in oncology.

Looking forward, multi-omics integration, artificial intelligence (AI)-driven target prediction, and adaptive clinical trial designs will be essential for refining the selection of repurposable candidates and tailoring therapies to individual patient profiles. Partnerships between academia, public health systems, and regulatory bodies will play a pivotal role in facilitating access and accelerating translational pipelines. With strategic investment and interdisciplinary collaboration, drug repurposing can evolve from an opportunistic practice to a mainstream pillar in precision oncology, particularly in resource-limited settings where cost-effective treatments are most urgently needed.

List of Abbreviations

FDA	Food and Drug Administration
TNBC	Triple-Negative Breast Cancer
HER2	Human Epidermal Growth Factor Receptor 2
ER	Estrogen Receptor
PR	Progesterone Receptor

VEGFR	Vascular Endothelial Growth Factor Receptor
PI3K	Phosphoinositide 3-Kinase
mTOR	Mammalian Target of Rapamycin
AMPK	AMP-Activated Protein Kinase
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
IGF-1R	Insulin-Like Growth Factor 1 Receptor
SGLT2	Sodium-Glucose Co-Transporter 2
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
BBB	Blood-Brain Barrier
CYP450	Cytochrome P450 (Enzyme Family)
GI	Gastrointestinal
MD	Molecular Dynamics
RMSD	Root Mean Square Deviation
ACE	Angiotensin-Converting Enzyme
ARB	Angiotensin II Receptor Blocker
CCB	Calcium Channel Blocker
Bcl-2	B-cell Lymphoma 2 (anti-apoptotic protein)
MCF-7	Michigan Cancer Foundation-7 (breast cancer cell line)
MDA-MB-231	Breast cancer cell line (Triple-negative subtype)
T47D	Human ductal breast epithelial tumor cell line
P-gp	P-glycoprotein

FAERS FDA Adverse Event Reporting System

References

1. WHO. 2021. Breast cancer: prevention and control. World Health Organization.
2. Khushalani, J. S., Cudhea, F. P., Ekwueme, D. U., Ruan, M., Shan, Z., Harris, D. M., Mozaffarian, D., & Zhang, F. F. 2022. Estimated economic burden of cancer associated with suboptimal diet in the United States. Cancer causes & control : CCC, 33(1), 73–80. https://doi.org/10.1007/s10552-021-01503-4
3. Bianchini, G., Balko, J. M., Mayer, I. A., Sanders, M. E., & Gianni, L. 2016. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nature reviews. Clinical oncology, 13(11), 674–690.
4. Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris, A., Sanseau, P., Cavalla, D., & Pirmohamed, M. 2019. Drug repurposing: progress, challenges and recommendations. Nature reviews. Drug discovery, 18(1), 41–58.
5. Ashburn, T. T., & Thor, K. B. 2004. Drug repositioning: identifying and developing new uses for existing drugs. Nature reviews. Drug discovery, 3(8), 673–683.
6. Viollet, B., Guigas, B., Sanz Garcia, N., Leclerc, J., Foretz, M., & Andreelli, F. 2012. Cellular and molecular mechanisms of metformin: an overview. Clinical science (London, England : 1979), 122(6), 253–270.
7. Pasquier, E., Ciccolini, J., Carre, M., Giacometti, S., Fanciullino, R., Pouchy, C., Montero, M. P., Serdjebi, C., Kavallaris, M., & André, N. 2011. Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment. Oncotarget, 2(10), 797–809. https://doi.org/10.18632/oncotarget.343
8. Chae, Y. K., Arya, A., Malecek, M. K., Shin, D. S., Carneiro, B., Chandra, S., Kaplan, J., Kalyan, A., Altman, J. K., Platanias, L., & Giles, F. 2016. Repurposing metformin for cancer treatment: current clinical studies. Oncotarget, 7(26), 40767–40780.
9. Dallakyan, S., & Olson, A. J. 2015. Small-molecule library screening by docking with PyRx. Methods in molecular biology (Clifton, N.J.), 1263, 243–250.
10. Chong, C. R., & Sullivan, D. J., Jr 2007. New uses for old drugs. Nature, 448(7154), 645–646.

11. Li, Y. Y., & Jones, S. J. 2012. Drug repositioning for personalized medicine. Genome medicine, 4(3), 27.
12. Nosengo N. 2016. Can you teach old drugs new tricks?. Nature, 534(7607), 314–316.
13. Oprea, T. I., Bauman, J. E., Bologa, C. G., Buranda, T., Chigaev, A., Edwards, B. S., Jarvik, J. W., Gresham, H. D., Haynes, M. K., Hjelle, B., Hromas, R., Hudson, L., Mackenzie, D. A., Muller, C. Y., Reed, J. C., Simons, P. C., Smagley, Y., Strouse, J., Surviladze, Z., Thompson, T., … Sklar, L. A. 2011. Drug Repurposing from an Academic Perspective. Drug discovery today. Therapeutic strategies, 8(3-4), 61–69.
14. Pantziarka, P., Bouche, G., Meheus, L., Sukhatme, V., Sukhatme, V. P., & Vikas, P. 2014. The Repurposing Drugs in Oncology (ReDO) Project. Ecancermedicalscience, 8, 442.
15. Pantziarka, Pan & Sukhatme, Vidula & Meheus, Lydie & Sukhatme, Vikas & Bouche, Gauthier. 2017. Repurposing non-cancer Drugs in Oncology – How many drugs are out there?. 10.1101/197434.
16. Sleigh, Sara & Barton, Cheryl. 2010. Repurposing Strategies for Therapeutics. Pharmaceutical Medicine. 24. 151-159. 10.1007/BF03256811.
17. Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. 2011. Molecular docking: a powerful approach for structure-based drug discovery. Current computer-aided drug design, 7(2), 146–157.
18. Trott, O., & Olson, A. J. 2010. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry, 31(2), 455–461.
19. Friesner, R.A., Banks, J.L., Murphy, R.B., Halgren, T.A., Klicic, J.J., Mainz, D.T., Repasky, M.P., Knoll, E.H., Shaw, D.E., Shelley, M., Perry, J.K., Francis, P. and Shenkin, P.S.A. 2004 New approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. Journal of Medicinal Chemistry, 47, 1739-1749. doi:10.1021/jm0306430
20. Hollingsworth, S. A., & Dror, R. O. 2018. Molecular Dynamics Simulation for All. Neuron, 99(6), 1129–1143.
21. Baselga, J., & Swain, S. M. 2009. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nature reviews. Cancer, 9(7), 463–475.
22. Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., & Zoete, V. 2014. SwissTargetPrediction: a web server for target prediction of bioactive small molecules. Nucleic acids research, 42(Web Server issue), W32–W38.

23. Kuhn, M., von Mering, C., Campillos, M., Jensen, L. J., & Bork, P. 2008. STITCH: interaction networks of chemicals and proteins. Nucleic acids research, 36(Database issue), D684–D688.
24. DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of health economics, 47, 20–33.
25. Kinnings, S. L., Liu, N., Tonge, P. J., Jackson, R. M., Xie, L., & Bourne, P. E. 2011. A machine learning-based method to improve docking scoring functions and its application to drug repurposing. Journal of chemical information and modeling, 51(2), 408–419.
26. Daina, A., Michielin, O. and Zoete, V. 2017 SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. Scientific Reports, 7, Article No. 42717.
27. Pires, D.E., Blundell, T.L. and Ascher, D.B. 2015 pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. Journal of Medicinal Chemistry, 58, 4066-4072.
28. Yang, H., Lou, C., Sun, L., Li, J., Cai, Y., Wang, Z., et al. 2018 Admetsar 2.0: Web-Service for Prediction and Optimization of Chemical ADMET Properties. Bioinformatics, 35, 1067-1069.
29. Pollak M. N. 2012. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer discovery, 2(9), 778–790.
30. Rumi, M. A., Sato, H., Ishihara, S., Kawashima, K., Hamamoto, S., Kazumori, H., Okuyama, T., Fukuda, R., Nagasue, N., & Kinoshita, Y. 2001. Peroxisome proliferator-activated receptor gamma ligand-induced growth inhibition of human hepatocellular carcinoma. British journal of cancer, 84(12), 1640–1647.
31. Alblowy, A. H., Maan, N., & Ibrahim, A. A. 2023. Optimal control strategies for SGLT2 inhibitors as a novel anti-tumor agent and their effect on human breast cancer cells with the effect of time delay and hyperglycemia. Computers in biology and medicine, 166, 107552.

32. Lampros, M., Vlachos, N., Lianos, G. D., Bali, C., & Alexiou, G. A. 2025. Editorial: Drug repurposing for cancer treatment: current and future directions. Frontiers in oncology, 15, 1550672.
33. Pasquier, E., André, N., Street, J., Chougule, A., Rekhi, B., Ghosh, J., Philip, D. S. J., Meurer, M., MacKenzie, K. L., Kavallaris, M., & Banavali, S. D. 2016. Effective Management of Advanced Angiosarcoma by the Synergistic Combination of Propranolol and Vinblastine-based Metronomic Chemotherapy: A Bench to Bedside Study. EBioMedicine, 6, 87–95.
34. Deshayes, F., & Nahmias, C. 2005. Angiotensin receptors: a new role in cancer?. Trends in endocrinology and metabolism: TEM, 16(7), 293–299.
35. George, A. J., Thomas, W. G., & Hannan, R. D. 2010. The renin-angiotensin system and cancer: old dog, new tricks. Nature reviews. Cancer, 10(11), 745–759.
36. Galligioni, E., & Ferro, A. 2001. Angiogenesis and antiangiogenic agents in non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands), 34 Suppl 4, S3–S7.
37. Perou, C. M., Sørlie, T., Eisen, M. B., van de Rijn, M., Jeffrey, S. S., Rees, C. A., Pollack, J. R., Ross, D. T., Johnsen, H., Akslen, L. A., Fluge, O., Pergamenschikov, A., Williams, C., Zhu, S. X., Lønning, P. E., Børresen-Dale, A. L., Brown, P. O., & Botstein, D. 2000. Molecular portraits of human breast tumours. Nature, 406(6797), 747–752.
38. Mukohara T. 2015. PI3K mutations in breast cancer: prognostic and therapeutic implications. Breast cancer (Dove Medical Press), 7, 111–123.
39. Viollet, B., Guigas, B., Sanz Garcia, N., Leclerc, J., Foretz, M., & Andreelli, F. 2012. Cellular and molecular mechanisms of metformin: an overview. Clinical science (London, England : 1979), 122(6), 253–270.
40. Ferrara N. 2002. VEGF and the quest for tumour angiogenesis factors. Nature reviews. Cancer, 2(10), 795–803.
41. Grivennikov, S. I., Greten, F. R., & Karin, M. 2010. Immunity, inflammation, and cancer. Cell, 140(6), 883–899.
42. Zhuang, Y., & Miskimins, W. K. 2011. Metformin induces both caspase-dependent and poly(ADP-ribose) polymerase-dependent cell death in breast cancer cells. Molecular cancer research : MCR, 9(5), 603–615.
43. Hirsch, H. A., Iliopoulos, D., Tsichlis, P. N., & Struhl, K. 2009. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer research, 69(19), 7507–7511.

44. Pires, D.E., Blundell, T.L. and Ascher, D.B. 2015 pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. Journal of Medicinal Chemistry, 58, 4066-4072.

45. Sarraf, P., Mueller, E., Jones, D., King, F. J., DeAngelo, D. J., Partridge, J. B., Holden, S. A., Chen, L. B., Singer, S., Fletcher, C., & Spiegelman, B. M. 1998. Differentiation and reversal of malignant changes in colon cancer through PPARgamma. Nature medicine, 4(9), 1046–1052.
46. Waring, M. J., Arrowsmith, J., Leach, A. R., Leeson, P. D., Mandrell, S., Owen, R. M., Pairaudeau, G., Pennie, W. D., Pickett, S. D., Wang, J., Wallace, O., & Weir, A. 2015. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nature reviews. Drug discovery, 14(7), 475–486.
47. Scafoglio, C., Hirayama, B. A., Kepe, V., Liu, J., Ghezzi, C., Satyamurthy, N., Moatamed, N. A., Huang, J., Koepsell, H., Barrio, J. R., & Wright, E. M. 2015. Functional expression of sodium-glucose transporters in cancer. Proceedings of the National Academy of Sciences of the United States of America, 112(30), E4111–E4119.
48. Murugan, S., Rousseau, B., & Sarkar, D. K. 2021. Beta 2 Adrenergic Receptor Antagonist Propranolol and Opioidergic Receptor Antagonist Naltrexone Produce Synergistic Effects on Breast Cancer Growth Prevention by Acting on Cancer Cells and Immune Environment in a Preclinical Model of Breast Cancer. Cancers, 13(19), 4858.
49. Friis, S., Sørensen, H. T., Mellemkjaer, L., McLaughlin, J. K., Nielsen, G. L., Blot, W. J., & Olsen, J. H. 2001. Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based cohort study in Denmark. Cancer, 92(9), 2462–2470.
50. Galligioni, E., & Ferro, A. 2001. Angiogenesis and antiangiogenic agents in non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands), 34 Suppl 4, S3–S7.
51. He, X., Esteva, F. J., Ensor, J., Hortobagyi, G. N., Lee, M. H., & Yeung, S. C. 2012. Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology, 23(7), 1771–1780.
52. Melhem-Bertrandt, A., Chavez-Macgregor, M., Lei, X., Brown, E. N., Lee, R. T., Meric-Bernstam, F., Sood, A. K., Conzen, S. D., Hortobagyi, G. N., & Gonzalez-Angulo, A. M. 2011. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 29(19), 2645–2652.

53. Barron, T. I., Connolly, R. M., Sharp, L., Bennett, K., & Visvanathan, K. 2011. Beta blockers and breast cancer mortality: a population- based study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 29(19), 2635–2644. https://doi.org/10.1200/JCO.2010.33.5422